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INDIANAPOLIS, INDIANA

Register online: meetings.gi.org
2022 ACG’S IBD SCHOOL & ACG/VGS/ODSGNA REGIONAL POSTGRADUATE COURSE
SEPTEMBER 9-11, 2022 | WILLIAMSBURG LODGE
WILLIAMSBURG, VIRGINIA
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ACG 2022
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REGISTRATION IS OPEN!
REGISTER ONLINE: ACGMEETINGS.GI.ORG
Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.
MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 34 – Thursday, August 25, 2022
Update on the Management of Anticoagulants and Antiplatelet Guidelines
Faculty: Neena S. Abraham, MD, MSc (Epid), FACP
Moderator: Bryan G. Sauer, MD, MSc (Clin Res), FACP
Thursday, August 25th at Noon Eastern and NEW! 8pm Eastern!

Week 35 – Thursday, September 1, 2022
ID for the GI – GI Presentations of Unusual Infections
Faculty: Mark S. Riddle, MD, DrPH
Moderator: Freddy Caldera, DO, MS, FACP
Thursday, September 1st at Noon Eastern and NEW! 8pm Eastern!

Visit gi.org/ACGVGR to Register
Disclosures

Jasmohan S. Bajaj, MD, MS, FACG
Bausch: Grant/Research Support
Biovie: Grant/Research Support
Cosmo Pharmaceuticals: Grant/Research Support
Grifols: Grant/Research Support
Mallinckrodt Pharmaceuticals: Grant/Research Support
Norgine: Advisory Committee/Board Member (Ended October 1, 2021)
Sequana: Grant/Research Support

David E. Bernstein, MD, MACG
AbbVie: Consultant, Grant/Research Support
Contus: Grant/Research Support
CymaBay: Grant/Research Support
Gilead: Consultant, Grant/Research Support
Novartis: Grant/Research Support
Novo Nordisk: Grant/Research Support

*All of the relevant financial relationships listed for these individuals have been mitigated*
Acute-on-Chronic Liver Disease

Jasmohan S. Bajaj, MD, MS, FACG
Professor of Medicine,
Division of Gastroenterology, Hepatology and Nutrition
Virginia Commonwealth University and
Central Virginia Veterans Healthcare System
Richmond, Virginia

Acute-on-Chronic Liver Failure Clinical Guidelines

In patients with cirrhosis and chronic liver disease, acute-on-chronic liver failure is emerging as a major cause of mortality. These guidelines indicate the preferred approach to the management of patients with acute-on-chronic liver failure and represent the official practice recommendations of the American College of Gastroenterology. The scientific evidence for these guidelines was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation process. In instances where the evidence was not appropriate for Grading of Recommendations, Assessment, Development, and Evaluation, but there was consensus of significant clinical merit, “key concept” statements were developed using expert consensus. These guidelines are meant to be broadly applicable and should be viewed as the preferred, but not only, approach to clinical scenarios.

Am J Gastroenterol 2021;00:1–27. https://doi.org/10.14309/ajg.0000000000001595; published online XXX
Important questions

• What is acute on chronic liver disease or failure and how is it different from decompensated cirrhosis and from acute liver failure?
• How do we define and prognosticate patients with ACLF?
• What are the precipitants and potential prevention strategies?
• What are the individual organ failures that we need to focus on?
• Should ACLF patients be given priority for liver transplant?
• What are the future directions?

Case- ER presentation

• A 59-year-old man is brought to the emergency room (ER) by his wife for new onset confusion and increased abdominal girth. Past medical history is notable for uncontrolled diabetes, obesity, and social alcohol use.
• On examination he is afebrile, alert, and oriented only to place. Abdominal examination revealed a fluid wave.
• He has not sought outpatient care for 3 years, although he underwent emergency surgery for a strangulated inguinal hernia 6 weeks ago.
• At hospital discharge, a PPI was initiated for “prophylaxis”.
• Notable admission labs include a serum creatinine 1.3 mg/dL, bilirubin 2 mg/dL, albumin 3.1g/dL, INR 1.4, WBC count 7000/mL, and platelet count 105x10⁹/L.
Case- Initial Work-up

• The patient has been in the ER for 8 hours and is finally admitted with diagnoses of cirrhosis, ascites, and HE. He is started on lactulose with some improvement in mental status but still has asterixis the next morning.
• Fourteen hours after initial presentation, a diagnostic paracentesis shows spontaneous bacterial peritonitis (SBP).
• His serum creatinine and WBC count have increased to 1.8 mg/dL and 8600/mL respectively.
• The urinalysis is bland, and renal sonogram is normal. He is started on IV ceftriaxone 2gm daily and IV 25% salt-poor albumin.

Case- 48 hours later

• Still disoriented despite ceftriaxone for 48 hours, with new onset-shortness of breath.
• Creatinine is now 3.0mg/dL, sodium 130 mEq/L, bilirubin 3.5 mg/dL and INR 1.8.
• A repeat tap shows a <25% reduction in PMNs. Blood and ascitic fluid cultures from the ER are negative.
• IV norepinephrine is initiated (since terlipressin is not currently available in the US). Antibiotics are escalated to meropenem and vancomycin since the ascites PMNs have not decreased by ≥25%.
Case - Next Morning

- Tachypneic and hypoxic (SpO2: 91%) with a new RLL infiltrate
- Obtunded, anuric with a MAP of 45mmHg. He is transferred to the ICU with a serum creatinine of 4.8 mg/dL and WBC count of 15000/mL.
- Discussions regarding intubation, renal replacement therapy (RRT), and pressor support are undertaken with his wife. Since he now requires organ support to maintain perfusion, oxygenation, and is obtunded, he is a suboptimal candidate for liver transplantation
- Ultimately the patient passes away without liver transplant.

ACLF Guidelines to practice
AJG 2022

Dominoes fall rapidly if precipitants for ACLF are not recognized early
Pathogenesis and Definitions

Gut-liver changes and immune dysfunction

Albillos et al J Hep 2020, Bajaj et al NEJM 2021
Hepatic and extrahepatic organ failures

Acute Liver Failure

Precipitants:
1. Drugs
2. Viral hepatitis
3. Autoimmune
4. Wilson

Chronic liver disease (>F2)

Compensated cirrhosis

Type A ACLF

Type B ACLF

Type C ACLF

Jaundice
Ascites
Variceal bleeding
Hepatic encephalopathy

Decompensated cirrhosis

Hepatic and extrahepatic organ failures

Jalan R et al ACLF WGO Consensus Gastroenterology 2014

Organ | APASL ACLF Research Consortium | EASL CLIF-C ACLF | NACSELD
--- | --- | --- | ---
Liver | Total Bilirubin PT/INR | Total bilirubin PT/INR | --
Kidney | Creatinine | Creatinine/Dialysis | Dialysis
Brain | HE grade | HE grade | HE grade III/IV
Circulatory | Lactate | MAP, vasopressors | MAP, vasopressors
Respiratory | -- | PaO₂ or SpO₂ / FiO₂ | Mechanical ventilation

Major Organ failure Category

Predominantly Hepatic failure variables

Combination of hepatic and extrahepatic organ failure variables

Predominantly extra-hepatic organ failure variables

Issues

Diagnosis can be made early enough for intervention to alter disease course.
Sensitive but not specific for early mortality

Diagnosis of ACLF may be made too late to impact disease outcome.

Diagnosis of ACLF may be made too late to impact disease outcome.
ACG ACLF definition

ACLF is a potentially reversible condition in patients with chronic liver disease with or without cirrhosis that is associated with the potential for multiple organ failure and mortality within 3 months in the absence of treatment of the underlying liver disease, liver support, or liver transplantation.

Bajaj JS et al ACG ACLF Guidelines 2021

ACG Guideline Concept Statements

1. In patients with cirrhosis who are hospitalized, the NACSELD score is likely associated with futility while the EASL-CLIF SOFA score is associated with 28-day prognostication.
2. None of the three society definitions is optimal for informing management change.
3. Prognostic markers that predict ACLF outcome should be separate from diagnostic markers that confirm the presence of ACLF.
4. Microbial composition and microbial-origin metabolites can be used as biomarkers for ACLF development and prognosis with further validation.

Bajaj JS et al ACG ACLF Guidelines 2021
Individual Organ Failures

Brain Failure or Acute Encephalopathy: Mostly HE

- Stabilize airway, BP
- Triage appropriately
- Lab work
- IV fluids, NG, antibiotics empirically if indicated

- Drug screen
- Psychiatric disorders
- Neurological disorders
- Delirium on dementia
- Infections

Initiate general care
Evaluate for alternatives
Commence empirical therapy for HE
Identify precipitating factors and reverse

- Lactulose either PO or via NG or via enemas depending on mentation
- Other therapies for HE improvement

- Infections
- GI bleeding
- Electrolyte disorder
- Diuretic overdose
- Unidentified

Acharya et al Am J Gastro 2018
• In ACLF, use of short-acting dexmedetomidine for sedation vs other agents to shorten time to extubation.
• In ventilated patients, we suggest against prophylactic antibiotics to reduce mortality or duration of mechanical ventilation.

AKI Definition
Increase in sCr 0.3 mg/dl ≤48 hours or 50% increase from baseline

<table>
<thead>
<tr>
<th>AKI Staging</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1: Increase in sCr 0.3 mg/dl in ≤48 hours</td>
<td>OR Increase in sCr ≥1.5-2.0 times from baseline</td>
</tr>
<tr>
<td>Stage 2: Increase in sCr ≥2.0-3.0 times from baseline</td>
<td>Stage 3: Increase in sCr ≥3.0 times from baseline OR Serum creatinine 4.0mg/dl with an acute increase of 0.3 mg/dl OR Initiation of renal replacement therapy</td>
</tr>
</tbody>
</table>

HRS-AKI

- Cirrhosis and ascites;
- Stage 2 or 3 AKI;
- No improvement of serum creatinine (decrease of creatinine ≤ 0.3mg/dl of baseline) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (1 g/kg body weight/day for 2 days);
- Absence of hypovolemic shock or severe infection requiring vasoactive drugs to maintain arterial pressure;
- No current or recent treatment with nephrotoxic drugs;
- Proteinuria <500 mg/day and no microhematuria (<50 RBCs/ml).
Terlipressin increases HRS reversal

- No overall survival benefit but trend for improved RRT-free survival and significant improvement in post-OLT survival
- Serum creatinine > 5 mg/dl associated with low response and increased deaths (70 vs 47%) with terlipressin
- Reduced need for RRT with terlipressin

Wong et al, NEJM 2021

1. In AKI stage 2 & 3 acute kidney injury (AKI), we suggest IV albumin and vasoconstrictors vs albumin alone
2. In hospitalized patients HRS-AKI without high grade of ACLF or major cardiopulmonary or vascular disease, we suggest terlipressin or norepinephrine to improve renal function.

Wong et al 2016, Wong et al NEJM 2021
Coagulation Failure: INR is not the be-all and end-all

1. In ACLF, we suggest against INR to measure coagulation risk
2. In patients with ACLF and altered coagulation parameters, we suggest against transfusion in the absence of bleeding or a planned procedure.
3. In patients who require invasive procedures, we recommend the use of Thrombo-elastography (TEG) or rotational TEG (ROTEM), vs INR, to accurately assess transfusion needs.

Precipitating Factors

• Infections
• Alcohol-related
• Surgery (Mayo Clinic and Vocal Penn Score)
• Drug-induced liver injury
• Viral hepatitis, including reactivation and flare
Infections lead to high mortality in cirrhosis

30% die within 1 month  Additional 30% die by 1 year

Clues that can indicate infections in cirrhosis

• Usual signs of infection may be absent due to impaired immune response
• Other signs and symptoms could be relevant
  – Altered mental status or hepatic encephalopathy
  – Acute kidney injury
  – Asymptomatic patients with ascites can have “silent” SBP
  – Increase in WBC count may not be dramatic since cirrhotic patients have a lower baseline
Virtual Grand Rounds

Any of the following criteria:
- MAP ≤ 65 mm Hg AND Lactate ≥ 2 mmol/L despite volume resuscitation
- Oxygen saturation < 90%
- Heart rate < 40 or > 130/min
- Respiratory rate < 10 or > 28/min
- Persistent decrease in level of consciousness

• Paracentesis with cell count
• Culture blood, ascitic fluid, urine
• Chest x-ray
• Stool toxigenic C. difficile (if patient has ≥ 3 unformed stools)

• Asciites PMN > 250/mm³

Pneumonia
- Community Acquired
- HCA
- Nosocomial

Urinary tract infection
- Antibiotics

Symptom resolution
- Clinical resolution
- Clinical and radiological resolution

Repeat paracentesis at 48 hours to confirm PMN decrease by 25%

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</table>

Piperacillin Tazobactam 4.5 g Q 6H
Vancomycin 125 mg PO Q 6H for 10 days

≥ 3 Unformed stool
Toxigenic C. difficile in stool
Positive blood culture
Blood stream infection

Any of the following criteria:
- MAP ≤ 65 mm Hg AND Lactate ≥ 2 mmol/L despite volume resuscitation
- Oxygen saturation < 90%
- Heart rate < 40 or > 130/min
- Respiratory rate < 10 or > 28/min
- Persistent decrease in level of consciousness

Transfer to ICU++

Timing of Antimicrobial Therapy: Impact on Survival

![Bar chart showing the impact of timing of antimicrobial therapy on survival.](chart.png)

- P = 0.008
- P < 0.001

Mortality (%) vs. Time from onset of shock to antibiotics

0-3 hours, 3-6 hours, 6-12 hours, 12-24 hours, > 24 hours
Inappropriate antibiotics increase mortality

- **Risk factor: Multidrug resistance organism**

  Arabi YM et al. Hepatology, Accepted 2012

Judicious use of albumin prevents mortality and AKI in SBP but not in other infections and not for all inpatients

ACG ACLF Guideline Recommendations: Infections

• Check for infection in hospitalized patients.
• In suspected infection, we suggest early antibiotics
• In patients not responding to antibiotic therapy, we recommend suspicion of a resistant organism or fungal infection
• In SBP albumin with antibiotics to prevent AKI and subsequent organ failures but not in other infections.
• In with prior SBP, we suggest use of antibiotics for secondary SBP prophylaxis to prevent recurrent SBP.
• In those needing primary SBP prophylaxis, we suggest daily prophylactic antibiotics, although no one specific regimen is superior to another, to prevent SBP
• We suggest avoiding PPI unless there is a clear indication

Therapeutic strategies

• General (airway, multi-disciplinary team, nutrition, treating precipitating factors)
• Specific treatments (albumin, G-CSF, Stem cell therapy)
• Liver-assist devices (MARS, ELAD)
• Liver transplant (deceased or living donor)
Transfer to ICU++

Paracentesis, Culture blood, ascitic fluid, urine, Chest x-ray

Treat infection

Vancomycin 15 mg/kg Q 6 H
Meropenem 1 gram Q 8 H

Enteral nutrition is preferred
Fluid resuscitation within 3 hours
Therapeutic paracentesis
Aspiration precautions
DVT prophylaxis
Stress ulcer prophylaxis

General measures

MAP <60 mg Hg
Norepinephrine Range: 0.125 to 0.2 mcg/kg/minute

MAP <60 Hg
Hydrocortisone 50 mg Q 6 h
Persistent shock

End of life care

If no resolution or condition worsens after initial Rx

Family Meeting/Decision

InVESTIGATIONS

Bajaj JS et al NEJM 2021

Albumin in Inpatients with Cirrhosis: Not Helpful

- 777 inpatients across multiple UK Centers
- Open-label randomized trial
- Albumin targeted to 3g/dl or standard of care for 14 days

Primary Endpoint: new infection, kidney dysfunction, or death between days 3 and 15 after the initiation of treatment.
Results: No significant change but higher respiratory failure in albumin arm

ACG Recommendations: We recommend against daily infusion of albumin to maintain albumin >3 gm/dl to improve mortality, prevention of renal dysfunction or infection

China et al NEJM 2021
G-CSF and effect on liver disease severity

176 patients randomized 1:1
Survival 34.1% vs 37.5% SMT, p=0.81
Terminated early due to futility

ACG Recommendations: In ACLF, we suggest against the use of G-CSF to improve mortality

Kedarisetty CK et al Gastro 2015, Engelmann et al J Hepatol 2021

Should ACLF patients get extra listing priority for liver transplant?
Arguments against prioritizing

1. Potential for misclassification of UNOS data vs ACLF grade
2. Using retrospective data to make prospective decisions
3. Zero-sum game; non-ACLF pts may be affected
4. Currently there is low support to change listing and priority criteria

Goldberg & Bajaj Liver Transpl 2021, Bajaj & Verna Liver Transpl 2020

Arguments for transplanting selected ACLF patients

1. MELD may not capture the disease severity
2. Acceptable survival post-LT for ACLF-2 and 3
3. Futility rules may need to be specified

TAM score:
- a. Age ≥53 years,
- b. arterial lactate ≥4 mmol/L
- c. mechanical ventilation with \( \frac{PaO_2}{FiO_2} \leq 200 \) mm Hg,
- d. leukocyte count ≤10 G/L

Jalan et al J Hepatol 2021, Artzner et al AJT 2020
Transplant versus Futility for ACLF: ACG Guideline recommendations

• ACLF patients who continue to require mechanical ventilation due to ARDS or brain-related conditions despite optimal therapy, we suggest against LT listing

• In patients with end-stage liver disease admitted to the hospital, we suggest early goals of care discussion and if appropriate, referral to palliative care to improve resource utilization

Bajaj JS et al ACG ACLF Guidelines 2021

Future Directions
What is needed in a biomarker for ACLF?

(a) objective,
(b) reliable,
(c) specific to ACLF and distinct from AD and from other patients without cirrhosis requiring critical care,
(d) easily translatable into clinical practice,
(e) determine who is a good candidate for liver transplantation.

Bajaj JS et al ACG ACLF Guidelines 2021

Issues with current ACLF definitions & biomarkers

- Discordance as to underlying liver disease severity and precipitating factors
- Not prognostic but diagnostic because end-organ failures are likely related to death
- Need to be more pro-active rather than reactive
1. Differentiate between patients with/without ACLF
2. Can independently predict who develops ACLF

Microbial-origin Metabolites

Back to the case: Opportunities missed that can snowball into ACLF

Bajaj JS et al Gastroenterology 2020, Moreau et al J Hepatol 2020
Suspect cirrhosis or chronic liver disease in appropriate patients

Precipitating factors:
- Alcohol
- Viral hepatitis
- DILI
- Surgery
- Ischemia
- Infection

Cirrhosis or Chronic Liver Disease

Hepatic and Extrahepatic Organ failure
OR
Acute on chronic Liver failure (ACLF)

Diagnose precipitating factors early

Early suspicion of infection
Early paracentesis & cultures
Appropriate antibiotics initially
Re-evaluate antibiotic therapy

Early transfer to prevent aspiration pneumonia

Resuscitate
Treat precipitating factor
Treat infection
Support failing organs

Assess for ICU management

Early consideration for Liver transplant eligibility

-Transplant candidate
- Number of organ failures

Evaluate for liver transplant

Evaluate for palliative and end of life care

Early involvement of palliative care, family and transplant team

ACLF Guidelines to practice
AJG 2022

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Summary and Take-Home Messages

- ACLF represents an increasingly large healthcare and economic burden in the US with a high mortality
- Infections are one of the major reasons for ACLF, and their bacteriology of infections is changing radically.
- A high index of suspicion, flexible, rapid and appropriate antibiotics and prevention of acute kidney injury is required to prevent ACLF from infections
- Avoid unnecessary PPIs
- Need for systematic efforts to improve patient outcomes (risk factor modification, early diagnosis, effective treatment)
- Cost-effective strategies towards higher recovery, less mortality are needed, especially in the context of liver transplant

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Questions and Answers

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